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(54) Diclofenac sodium plaster.

(57) A diclofenac sodium plaster has a backing material and a paste spread on the backing material. The paste is composed of diclofenac sodium, a penetration enhancer composed of 1-menthol and propylene glycol, and a hydrophilic base composed principally of a water-soluble polymer.

EP 0 524 582 A1

polyacrylic acids and/or polyacrylate salts with multivalent metal compounds and that obtained by freezing and melting an aqueous solution of polyvinyl alcohol. They can be used either singly or in combination. These water-soluble polymers are preferably added in a total proportion of 0.5-40 wt.%, notably 1-20 wt.% based on a paste.

Propylene glycol added as a penetration enhancer is preferably added in a proportion of 0.1-60 wt.% based on the paste, with 0.5-20 wt.% being particularly preferred. 1-Menthol is preferably added in a proportion of 0.05-10 wt.%, especially 0.1-5 wt.% based on the paste.

According to the present invention, the combined use of propylene glycol and 1-menthol as a penetration enhancer can synergistically increase the percutaneous absorption of diclofenac sodium as will be demonstrated in examples to be set forth later. In addition to such a penetration enhancer, the plaster according to the present invention can also include one or more conventional absorption promoters such as oleic acid, oleyl alcohol, diisopropyl adipate, octyldodecanol, diethyl sebacate, benzyl alcohol, isopropyl myristate, crotamiton, lauryl alcohol, 2-octyldodecanol, ethyl 2-ethylhexanoate, calcium thioglycolate, capric monoglyceride, caprylate esters, caprate esters, decyl oleate, diethyl sebacate, squalane and/or D-limonene.

Besides the essential ingredients described above, the plaster according to the present invention may also include other additives incorporated in conventional hydrophilic-base-containing plasters, for example, polyhydric alcohols as moisturizing agents, such as glycerin and sorbitol; inorganic compounds as fillers, such as kaolin and titanium dioxide; and surfactants such as polyoxyethylene sorbitan monooleate, sorbitan monooleate, polyoxyethylene hydrogenated castor oil, polyoxyethylene lauryl ether and polyoxyethylene monolaurate; as well as, if necessary, perfumes, stabilizers, crosslinking agents, pH regulators, etc.

The plaster according to the present invention can be prepared, preferably, by formulating a paste from the above-described ingredients in a manner known *per se* in the art and then having the paste carried on a backing material.

The paste useful in the plaster of this invention preferably has a stress in a range of from 5×10^3 dyne/cm^2 to 5×10^5 dyne/cm^2, especially from 0.8×10^4 dyne/cm^2 to 1.0×10^5 dyne/cm^2. Incidentally, the stress of a paste is measured, for example, in the following manner. After the formulation of the ointment, it is placed in a cylindrical vessel whose diameter and height are 40 mm and 20 mm, respectively. After sealing the vessel, the vessel with the paste placed therein is maintained at 25 °C for at least 168 hours. The paste is then placed on a sample table of a compression tester (e.g., "SUN RHEO METER", trade mark; manufactured by K.K. Sun Kagaku), and its central part is pressed at a compression speed of 300 mm/min against a disk-shaped adapter having a diameter of 15 mm and mounted on a pressure-sensing shaft. The stress of the paste is measured in terms of the stress produced upon pressing the paste over a distance of 2 mm after the adapter has contacted the paste.

No particular limitation is imposed on the backing material as long as it is a woven fabric, non-woven fabric, film or sheet having flexibility. For example, a woven or non-woven fabric of rayon, polyester, polyolefin or polyurethane fibers, a polymer film, a foamed sheet, or the like can be used. They may be applied with an anchor coat, as needed.

No particular limitation is imposed on the preparation method of the plaster according to this invention. The plaster can be prepared by formulating a paste containing 0.5-20 wt.% of diclofenac sodium, spreading it on a backing material and then covering the surface of the paste with a protective film or, as an alternative, by formulating a paste containing 0.5-20 wt.% of diclofenac sodium and then sandwiching it between a backing material and a protective film.

The plaster obtained as described above may be stored in a tight container, envelope or the like, as needed.

The present invention will next be described by examples.

Example 1

To 15 g of propylene glycol heated to 40 °C in advance, 1 g of diclofenac sodium, 3 g of 1-menthol and 1 g of polyoxyethylene hydrogenated castor oil were added, followed by stirring into an intimate mixture (A). In 10 g of propylene glycol, 2.5 g of sodium carboxymethylcellulose, 6 g of sodium polyacrylate and 0.1 g of aluminum glycinate were uniformly dispersed (B). One gram of gelatin was dissolved in 27.68 g of purified water which had been heated to about 60 °C (C). 0.12 g of tartaric acid, 3.6 g of aqueous polyacrylic acid solution (10%), 30 g of D-sorbitol solution (70% aqueous solution), the mixture (A), the suspension (B) and the solution (C) were kneaded into an intimate paste, which was then spread at a rate of 0.1 g/cm^2 on a non-woven fabric. The surface of the paste was covered with a polyester film, whereby a diclofenac sodium plaster containing 1 mg of diclofenac sodium per cm^2 was obtained. The stress of the paste of the diclofenac sodium plaster was 1.8×10^4 dyne/cm^2 when measured by the method described above.

Comparative Example 6

A diclofenac sodium plaster containing 1 mg of diclofenac sodium per cm^2 was obtained in a similar manner to Example 4 except that purified water was added instead of 1-menthol.

Test 1

The diclofenac sodium plasters prepared in Example 1 and Comparative Examples 1, 2 and 3, respectively, were each applied to the shaved backs (30 cm^2 area) of three male guinea pigs (species: Hartley, age: 4 weeks old, body weight: 250-300 g). From each guinea pig, blood samples were collected through a cannula inserted in the carotid before the application of the plaster and upon elapsed times of 2, 4, 6 and 8 hours after the application of the plaster. The diclofenac concentrations in the plasmas of the respective blood samples were measured by HPLC, whereby changes in the diclofenac sodium concentration in plasma were observed. The results are diagrammatically shown in FIG. 1.

Test 2

The diclofenac sodium plasters prepared in Example 4 and Comparative Example 4, respectively, were each applied to the shaved backs (30 cm^2 area) of three male guinea pigs (species: Hartley, age: 4 weeks old, body weight: 250-300 g). From each guinea pig, blood samples were collected through a cannula inserted in the carotid before the application of the plaster and upon elapsed times of 2, 4, 6 and 8 hours after the application of the plaster. The diclofenac concentrations in the plasmas of the respective blood samples were measured by HPLC, whereby changes in the diclofenac sodium concentration in plasma were observed. The results are diagrammatically shown in FIG. 2.

As is evident from these results, excellent transdermal absorption is observed only when 1-methanol and propylene glycol are added in combination.

Claims

1. A diclofenac sodium plaster comprising a backing material and a paste spread on the backing material, said paste comprising diclofenac sodium, a penetration enhancer composed of 1-menthol and propylene glycol, and a hydrophilic base composed principally of a water-soluble polymer.

2. The plaster of claim 1, wherein dichlorofenac sodium is contained in an amount of 0.5-20 wt.% based on the paste.

3. The plaster of claim 1, wherein the water-soluble polymer is selected from the group consisting of polyacrylic acid, sodium polyacrylate, carboxyvinyl polymer, sodium carboxymethylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol, hydroxypropylcellulose, hydroxyethylcellulose, ethylcellulose, alginic acid, sodium alginate, and gelatin.

4. The plaster of claim 1, wherein the water-soluble polymer is contained in an amount of 0.5-40 wt.% based on the paste.

5. The plaster of claim 1, wherein propylene glycol is contained in an amount of 0.1-60 wt.% based on the paste.

6. The plaster of claim 1, wherein 1-menthol is contained in an amount of 0.05-10 wt.% based on the paste.

7. The plaster of claim 1, wherein the stress of the paste ranges from 5×10^3 to 5×10^5 dyne/cm^2.

8. The plaster of claim 1, wherein the backing material is a woven or non-woven fabric of rayon, polyester, polyolefin or polyurethane fibers, a polymer film, or a foamed sheet.

FIG. 1

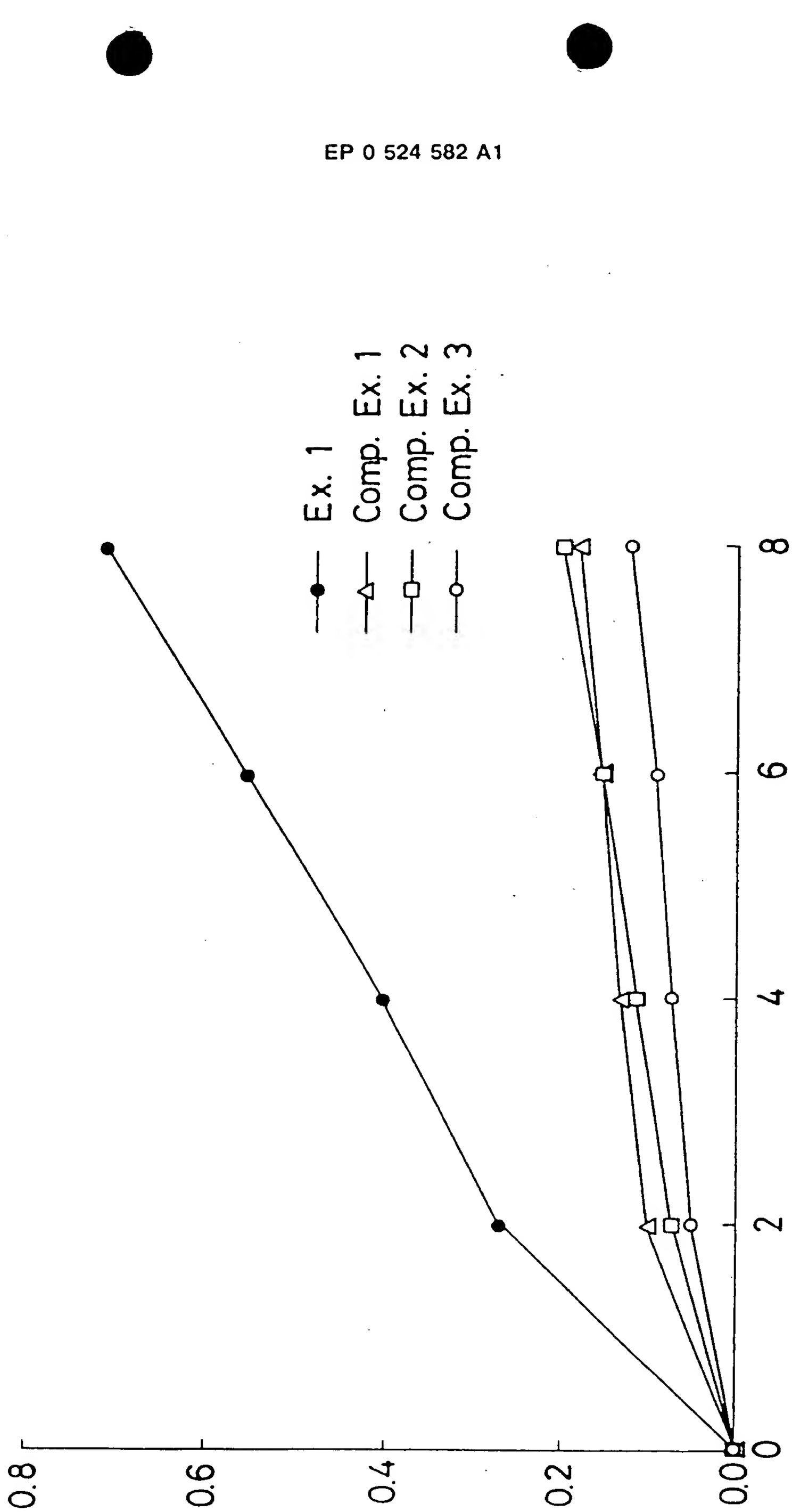
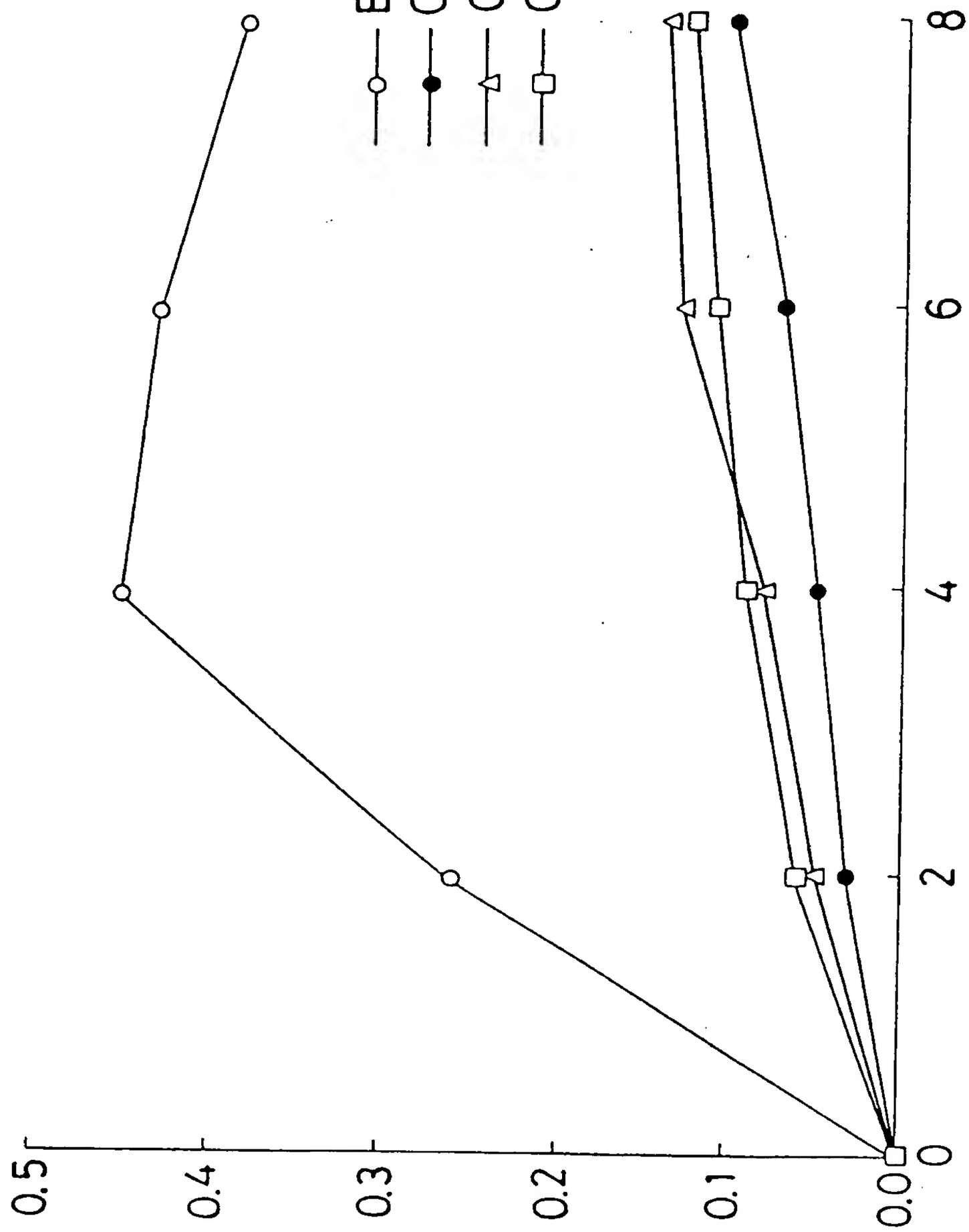

Ex. 1
Comp. Ex. 1
Comp. Ex. 2
Comp. Ex. 3
Diclofenac concentration in plasma (μg/mℓ)
0.0
0.2
0.4
0.6
0.8
0
2
4
6
8
Time (hrs)

FIG. 2


Ex. 4
Comp. Ex. 4
Comp. Ex. 5
Comp. Ex. 6
0.5
0.4
0.3
0.2
0.1
0.0
0
2
4
6
8
Time (hrs)
Diclofenac concentration in plasma (μg/mℓ)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 11 2382

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X Y	US-A-4 543 251 (TAKUZO KAMISHITA) * claims 1,4 * * column 2, line 21 - line 26 * * example 1 *	1-6 7,8	A61K31/195 A61K9/70 A61K47/10
Y	PATENT ABSTRACTS OF JAPAN 21 December 1984 & JP-A-59 227 819 (NITTO DENKI KOGIO KK) * abstract *	7,8	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	15 OCTOBER 1992	VENTURA AMAT A.

CATEGORY OF CITED DOCUMENTS

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